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Cells of periodontium: their role in the healing of wounds*

ANTONY H MELCHER MDS HDD PhD
Professor of Dentistry, and Associate Dean, Life Sciences, School of Graduate Studies, University of Toronto, Canada

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Some biological considerations

The periodontium is a connective tissue organ, protected by epithelium, that attaches the teeth to the bone of the jaws and provides a continually adapting apparatus for their support during function. It comprises four connective tissues, two of which are mineralised and two fibrous. The two mineralized connective tissues are the cementum that covers the roots of the teeth, and the alveolar bone that lines the sockets of the teeth. The fibrous connective tissues are the lamina propria of the gingiva and the periodontal ligament. Collagen fibres of both the lamina propria of the gingiva and the periodontal ligament are embedded in cementum, providing attachment for the teeth.

The periodontal ligament is, in many ways, a unique connective tissue. It is remarkably vascular and cellular for a fibrous connective tissue, and it contains within its fabric at least three distinct populations of connective tissues cells; populations of cells that express the phenotypes of fibroblasts, osteoblasts or cementoblasts *(1)*. Whether all three of these differentiated populations of cells take origin from a single population of ancestral cells, that is from a population of stem cells, or each of them from a different population of progenitor cells, the fate of whose progeny is already determined, is unknown *(2,3)*. In contrast, the connective tissue cells of the lamina propria of the gingiva can, to the best of our knowledge, express only the phenotype for fibroblasts *(4,5)*. This suggests that, under physiological conditions, only cells from periodontal ligament can synthesise and secrete cementum to attach newly-synthesised collagen fibres of periodontal ligament or lamina propria of gingiva to tooth (see below).

It has been shown that a small proportion of periodontal ligament cells are in mitosis at any given time *(3,6)*. The cells of the periodontal ligament are also highly active metabolically; those of the rat mandibular molar turn the collagen over ~5 times faster than do the fibroblasts in the lamina propria of the gingiva and ~15 times faster than the fibroblasts of skin *(7)*. Indeed, the collagen of periodontal ligament of rat mandibular molar has been calculated to have a half-life that could be as short as ~1 day *(8)*. Furthermore, the cells of periodontal ligament are continually remodelling periodontal ligament and modelling and remodelling alveolar bone and cementum *(9)*. This permits the width and integrity of the periodontal ligament to be maintained as the teeth assume new positions in the jaws in response to physiological, therapeutic and iatrogenic stimuli.

Wound healing

It was suggested some years ago that, because cementoblasts probably take origin exclusively from cells of periodontal ligament, new attachment of collagen fibres to the root of a tooth following periodontal surgery can occur only if cells of periodontal ligament colonise that part of the root surface where cementogenesis is required *(10)*. Furthermore, if regeneration of periodontium is being sought, that is restoration of the periodontium to the anatomical and functional state that existed prior to the onset of disease, the particular site in the wound to be restored by each of the individual tissues must be colonised during healing by the cells of that tissue. If the cells from an inappropriate tissue colonise a particular area of the wound, healing will lead to distortion in the anatomical form and, therefore, function of the organ. In this event regeneration will not have occurred but, instead, repair which describes restoration of tissue continuity without regard for anatomical form or function. For example, if epithelial cells migrate onto that part of the root surface where cementogenesis is required, no new attachment of fibres of lamina propria of gingiva or periodontal ligament to tooth can take place at that site; or if cells of lamina propria of gingiva colonise the site immediately coronal to the alveolar bone crest, no coronal regeneration of alveolar bone can be expected. The reasoning for this concept has been described in the so-called 'domain hypothesis' *(10)* for which there is now some experimental support *(4,11)*.

Central to regeneration of periodontium after surgical intervention in the treatment of periodontal diseases is the new attachment of collagen fibres of periodontal ligament and lamina propria of gingiva to the root of the tooth but this still cannot be achieved either predictably or reproducibly. However, I believe that it should be possible to meet this requirement in the foreseeable future. This is because it is now understood that if the surface of the root in the wound is demineralised to expose the collagen fibres of the organic matrix of the tooth, newly-deposited collagen fibres of periodontal ligament or lamina propria of gingiva can be 'spliced' to or interdigitated with the former by fibroblasts. This means that new attachment to the tooth can be achieved in the absence of newly-deposited cementum *(4,12,13,14)*. It consequently precludes the need for cementoblasts and their precursors to migrate to the root surface, to colonise all of that part of the root surface to which new attachment is required and to synthesise and deposit new cementum on those surfaces so that the ends of newly-synthesised collagen fibres of lamina propria or periodontal ligament can be trapped at the root surface. What is still needed is the guarantee that fibroblasts from lamina propria of gingiva and periodontal ligament will migrate to and colonise these surfaces when required. Theoretically this requirement should be achieved rather more readily than that for cementoblasts but there is still the problem of excluding epithelium from these sites. To do this we need to ensure that during the cell migration and attachment phase of healing, the epithelial cells are restricted to the coronal part of the root to which should be attached the newly-formed junctional epithelium. Migration of

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epithelial cells along or to the root surface apical of these limits will result in the development of a long junctional epithelium at the expense of newly-attached dentogingival fibres.

There is a small body of basic biological knowledge that supports the belief that demineralisation of the root surface constitutes a rational manoeuvre in periodontal surgery. It is well known that, in vitro, cultured connective tissue cells grow well on collagen substrates and we have shown that cultured gingival fibroblasts will form orientated systems more readily in relation to demineralised root surfaces than to those that have not been demineralised *(15,16)*. If fibroblasts and their precursors are to migrate to root surfaces then directionality must be imposed upon their migration from the site of their birth to the root surface (see, for example, *(2)*). This is most readily achieved through chemotactic attraction by appropriate substances acting at the site to which the cells must migrate (see, for example, *(17)*). Collagen has been shown to be chemotactic in vitro for fibroblasts *(18)*. Furthermore, fibronectin, which is also strongly chemotactic for fibroblasts and is present in plasma and therefore shed into the wound, binds with great affinity to collagen *(19)*. It appears that fibronectin may also bind with greater affinity in vitro to root slices that have been demineralised than to those that have not *(20)*. Finally, receptors for soluble Type I collagen have been demonstrated on fibroblasts and these may play a role in effecting the attachment of gingival or periodontal ligament fibroblasts to the collagen exposed by demineralising root surfaces *(21,22)*. All of these factors suggest that demineralisation of the root surface promotes migration to and attachment of fibroblasts to that site during wound healing in vivo.

Much remains to be learnt. It is not yet clear what are the surgical requirements for predictable and reproducible new attachment. For example it may be advantageous to 'glue' the gingival flap to the root surface and application of fibronectin to the cut surfaces may be useful for this purpose *(23)*. Similarly basic investigation could lead to methods of specifically altering different parts of the root surface so that fibroblasts and epithelial cells are attracted to different sites, and their attachment to these is promoted selectively. While a great deal of work remains to be done before new attachment of acceptable quality and distribution can be guaranteed following every surgical procedure, it is encouraging to know that we have some understanding of the biological basis of what we now do clinically, a situation that has not always pertained in surgical treatment of periodontal diseases.

References

1 Melcher AH. Periodontal Ligament. In, Orbans's Oral Histology and Embryology, Bhaskar SN, ed. 9th ed. C.V. St Louis: Mosby, 1980;208–13.

2 Gould TRL, Melcher AH, Brunette DM. Migration and division of projenitor cell populations in periodontal ligament after wounding. J Periodont Res 1980;15:20–42.

3 McCulloch CAG, Melcher AH. Cell density and cell generation in the periodontal ligament of mice. Am J Anat 1983;167:43–58.

4 Boyko GA, Melcher AH, Brunette DM. Formation of a new periodontal ligament by periodontal ligament cells implanted *in vivo* after culture *in vitro*. A preliminary study of transplanted roots in the dog. J Periodont Res 1981;16:73–88.

5 Nyman S, Karring T, Lindhe J, Planten S. Healing following implantation of periodontitis affected roots into gingival connective tissue. J Clin Periodontal 1980;6:394–401.

6 Roberts WE. Cell kinetic nature and diurnal periodicity of the rat periodontal ligament. Archs Oral Biol 1975;20:465–71.

7 Sodek J. A new approach to assessing collagen turnover by using a microassay. A highly efficient and rapid turnover of collagen in rat periodontal tissues. Biochem J 1976;160:243–6.

8 Sodek J. A comparison of the rates of synthesis and turnover of collagen and non-collagen proteins in adult rat periodontal tissues and skin using a microassay. Archs Oral Biol 1977;22:655–65.

9 Vignery A, Baron R. Dynamic histomorphometry of alveolar bone remodelling in the rat. Anat Rec 1980;196:191–200.

10 Melcher AH. On the repair potential of periodontal tissues. J Periodontal 1976;47:256–60.

11 Nyman S, Gottlow J, Karring T, Lindhe J. The regenerative potential of the periodontal ligament. An experimental study in the monkey. J Clin Periodontal 1982;9:257–65.

12 Register AA. Bone and cementum induction by dentin demineralized in situ. J Periodontal 1973;44:49–54.

13 Register AA, Burdick F. Accelerated reattachment with cementogenesis to dentin demineralized in situ. J Periodontol 1976;47:497–505.

14 Crigger M, Bogle G, Nilveus R, Egelberg J, Selvig KA. The effect of citric acid application on the healing of experimental furcation defects in dogs. J Periodont Res 1978;13:538–49.

15 Pitaru S, Melcher AH. Orientation of gingival fibroblasts and newly-synthesized collagen fibres *in vitro*. Resemblance to transseptal and dento-gingival fibres *in vitro*. J Periodont Res 1983;18:483–500.

16 Pitaru S, Gray A, Aubin JE, Melcher AH. The influence of the morphological and chemical nature of dental surfaces on the migration, attachment and orientation of human gingival fibroblasts *in vitro*. J Periodont Res 1984;19:408–18.

17 Shoshan S. Wound Healing. In: Hall DA, Jackson DS, eds International Review of Connective Tissue Research, 1981;9:1–26.

18 Postlethwaite AE, Seyer JM, Kang AH. Chemotactic attraction of human fibroblasts to type I, II and III collagens and collagen-derived peptides. Proc Natl Acad Sci USA 1974;75:871–75.

19 Kleinman HK, Klebe RJ, Martin GR. Role of collagenous matrices in the adhesion and growth of cells. J Cell Biol 1981;88:473–85.

20 Karp W, Sodek J, Aubin JE, Melcher AH. A comparison of the binding of fibronectin and laminin to mineralized tooth root surfaces. J Dent Res 1984;63:221 (Abstract).

21 Goldberg BD. Binding of soluble type 1 collagen molecules to the fibroblast plasma membrane. Cell 1979;16:265–75.

22 Goldberg BD. Binding of soluble type 1 collagen to fibroblasts: effect of thermal activation of ligand, ligand concentration, pinocytosis, and cytoskeletal modifiers. J Cell Biol 1982;95:747–51.

23 Caffesse R, Holden M, Kon S, Nasjleti C. Citric acid/fibronectin in treating periodontitis in Beagle dogs. J Dent Res 1984;63:221 (Abstract).